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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,093	GUENTHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-50 and 53-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-50 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-39, 51 and 52 have been canceled. Claims 40-50 and 53-57 are pending and under consideration in the instant office action.

Applicant's arguments filed 7-18-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendment filed 7-18-05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The addition of the application numbers into the paragraph beginning on pg 10, line 9, is new matter. No support for the patent applications is found in the specification as originally filed. The applicants cannot newly incorporate entire patent applicants into the specification by reference. The disclosures of the applications contain a greater scope than originally contemplated in the instant application. It is not readily apparent that the disclosures of the applications newly cited were originally intended to be incorporated by reference in their entirety into the instant application. Applicant is required to cancel the new matter in the reply to this Office Action.

Applicants have added US Patent application 09/954,483 and deleted US Patent application 60/232,957 in the paragraph bridging pg 10-11 in the amendment filed 7-18-05. The changes were not marked in the amendment. The disclosures of 09/954,483 and 60/232,957 are different in scope; therefore, the amendment is new matter. If application 09/954,483 is the same as 60/232,957, the specification will need updated to indicate that application 09/954,483 has been allowed as US Patent 6,929,909.

Claim Rejections - 35 USC § 101

Claims 40-50 and 53-57 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 40-50 and 53-57 are directed toward a transgenic mouse whose genome comprises a null allele of the endogenous mCAR2 gene.

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf

> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

> "Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably

confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

The mCAR2 gene

"An additional member of this superfamily, constitutive activator of retinoid acid response (CAR) receptors, has been described (See, e.g. , U.S. 5,756,448). It has been suggested that CAR could play an important role in the regulatory network that controls expression of RA responsive genes. Recently. a new murine orphan member, termed mCAR was identified which is closely' related to the previously identified human orphan CAR (hCAR) (See e.g., Choi, et al., J.

> Biol. Chem. 272(38)23565-71(1997)). Like hCAR, mCAR expression is highest in the liver. Both mCAR 1 and hCAR are apparently constitutive transcriptional activators. This activity is dependent on the presence of the conserved C-terminal AF-2 transcriptional activation motif. As expected from its inability to bind DNA, the mCAR2 variant neither transactivates by itself nor inhibits transactivation by hCAR or mCAR1" (paragraph bridging pg 1-2).

The art did not teach the function of the mCAR2. One of skill would not have reasonably implied that mCAR2 disruptions were associated with any disease at the time of filing.

The specification teaches making mCAR2 -/+ and -/- mice with a deletion of bp 282-403 (121 bp) of the mCAR2 gene (pg 51-52; Example 1; Fig. 2). It is noted that the specification does not teach what promoters drive the LacZ and neo genes inserted into the mCAR2 gene, that the 121 bp from 282-403 provide the function of mCAR2 or that a mCAR2 gene having the 121 bp deletion produces a non-functional mCAR2 protein.

The specification suggests doing expression analysis using the mice pg 53, line 23. RNA transcripts were detectable in the liver, gallbladder, adrenal gland, small intestine and cecum (pg 53, lines 23-29). Using the mice claimed for expression analysis is not a substantial utility because many tissues expressed the transgene and because the results did not reveal the function of the mCAR2 gene.

The specification suggests using the mice as a model of disease, specifically as a model for infertility, glucose metabolism, diabetes, behavioral, neurological, neuropsychological, psychotic phenotypes (pg 18-20; pg 20, line 2). However, the specification does not disclose that neurological, neuropsychological or psychotic disease found in humans is linked to a disruption in the nuclear hormone receptor of SEQ ID NO:1. The mice had

abnormalities in the spleen, thymus and lymph nodes (pg 52-53); however, the specification does not teach how to use such mice as a model of disease. The mice showed decreased performance in the rotarod test. However, the specification does not teach how to use such mice as a model of any disease or that a disruption in SEQ ID NO: 1 in humans relates to a disease that causes decreased coordination. None of the phenotypes found by the tests correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SEQ ID NO: 1. The results of the behavioral tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate nuclear hormone receptor expression because nuclear hormone receptor is not expressed in the cells of the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having the phenotypes recited in claims 39-50.

The medical profession does not treat organs having decreased size or weight; therefore, treating organ size or weight is not a substantial or credible utility. Nor are

organs having decreased size or weight specific to any disease; therefore, treating organ size is not a specific utility.

The medical profession does not treat organ to body weight ratio; therefore, treating organ to body weight ratio is not a substantial or credible utility. Nor is organ to body weight ratio specific to any disease; therefore, treating organ to body weight ratio is not a specific utility.

The medical profession does not treat spleens, thymuses or lymph nodes having lymphoid depletion; therefore, treating spleens, thymuses or lymph nodes having lymphoid depletion is not a substantial or credible utility. Nor are spleens, thymuses or lymph nodes having lymphoid depletion specific to any disease; therefore, treating organ size is not a specific utility. While patients having decreased lymphoid cells are treated as a whole, the spleens, thymuses and lymph nodes are not specifically treated; therefore, targeting the increase of lymphoid cells to spleens, thymuses or lymph nodes is not credible.

The asserted utilities for a mouse having impaired coordination are not specific, substantial or credible. First, the medical profession does not specifically treat impaired coordination. For example, impaired coordination in the elderly may occur and may be caused by osteoporotic bones, symptoms of pain, or atrophied muscles. The osteoporotic bones, symptoms of pain or atrophied muscles would be treated, not the impaired coordination. Furthermore, "impaired coordination" is a relative term. Second, the medical profession does not treat clumsiness. For example, a first tennis player may have impaired coordination, or lower than average coordination (clumsy), while the

second tennis player has better than average coordination. The specification does not teach how to treat the first player so that the first player would be as coordinated as the second player. Treating clumsiness cannot be envisioned; therefore, using the mouse as a model for clumsiness is not a substantial or credible utility. In addition, the rotarod test used to determine impaired coordination is used to test gross neurological function; therefore, using mice with impaired coordination is not specific to any neurological condition. Overall, mice having impaired coordination do not have a specific, substantial or credible.

In addition, a mouse having a small or light thymus, spleen, lymph node is not specific to any disease condition. A mouse having decreased coordination/balance is not specific to any disease. A disruption in a mCAR2 gene has not been linked to any disease condition. Therefore, the mice are not models of any disease.

Wild-type mice could be used to determine agents that make organs bigger or heavier. Wild-type mice could be used to determine agents that improve coordination. Therefore, using mice to find agents that increase organ size/weight or coordination/balance is not specific to mice having a disruption in the mCAR2 gene as claimed. In addition, the specification does not teach identifying any therapeutic agents using the mice; therefore, applicants' assertion is not credible in view of the teachings in the art and the lack of examples in the specification.

The data provided in the specification is not substantial because the observed phenotypes may have been a result of the donating ES cell phenotype and cannot be compared to a C57Bl6 wild-type control mouse. The Jackson Laboratory describes

C57BL/6 mice as having a high susceptibility to diet-induced obesity and type 2 diabetes (see www.jax.com under "Description of mouse strains," stock number 000664). The mice in the examples of the specification were of a mixed strain (F2 homozygotes were 75% C57Bl/6 and 25% 129/OlaHsd). The specification does not teach which generation of mice were tested or to what wild-type control they were compared. If the homozygous F2 mice were compared to a C57Bl/6 wild-type control, the phenotype of the 129/OlaHsd strain may have contributed to the observed difference in the phenotype and not the disruption of the mCAR2 gene. Crabbe of record supports the examiners position by teaching that C57Bl/6 mice have different phenotypes than other strains of mice (Science, June 4, 1999, Vol. 284, pg 1670-1672). Therefore, a mixed strain knockout mouse may have a phenotype that is found in the contributing ES cell strain and not in the wild-type C57Bl6 mouse. The specification does not teach the mixed strain knockout mouse was backcrossed adequately for a proper comparison to a wild-type C57Bl6 mouse. The specification does not teach the mixed strain knockout mouse was backcrossed adequately for a proper comparison to a wild-type C57Bl6 mouse. The specification does not teach that both wild-type C57Bl/6 and the wild-type contributing ES cell strain had the same body weight. As such, one of skill would not be able to conclude that the observed difference was attributed to the knockout of mCAR2 and not the 129/OlaHsd genotype of the ES cell strain contributing to the genome of the heterozygous mice. Thus, the mice claimed do not have substantial utility because the data provided is not substantial.

The specification asserts the mice claimed are used as a model of disease relating to disruptions in mCAR2. The asserted utility is not substantial, specific or credible because the phenotypes claimed do not reflect a disease state in humans. No diseases in humans are caused by a disruption in mCAR2. Therefore, the asserted utility of using the mouse as a model of disease is not substantial or specific.

The specification asserts the mice claimed are used to determine compounds that modulate mCAR2 expression. The asserted utility is not credible because mCAR2 is not expressed in the mice and because compounds found using such a mouse may act on non-mCAR2 proteins in a pathway related to mCAR2.

The specification asserts the mice claimed are used to determine compounds that ameliorate a particular phenotype. The asserted utility is not specific, substantial or credible for reasons in the following paragraphs.

Determining compounds that ameliorate a phenotype is not a specific utility because the specification does not link any of the phenotypes described in the specification to any specific disease or to a disease caused by a mCAR2 disruption in humans.

In fact, the phenotypes observed in the Examples may be a result of other genes compensating for the disruption of mCAR2. Olsen taught that a disruption of a gene in a mouse does not necessarily correlate to or cause the phenotype observed in the mouse because other proteins compensate for the disruption (Olsen, GABA in the Nervous System, 2000, pg 81-95; "This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products" pg

82, last 11 lines of col. 1). Therefore, determining compounds that ameliorate the phenotypes observed in the Examples would not be a specific or substantial utility because the phenotypes observed in the Examples are not necessarily caused by the disruption of mCAR2.

For example, Srivastava (PNAS, Nov. 23, 1999, Vol. 96, No. 24, pg 13783-13788) taught making an ANX7 -/- mouse with defects in insulin secretion and that the observed phenotype was a result of compensation by making more secreting cells and loading each secretory granule with more insulin" (pg 13788, last full ¶). Therefore, observed phenotypes in the instant application may be a result of cells compensating for the lack of mCAR2 and not a result of the disruption of the mCAR2 gene.

Determining compounds that ameliorate a phenotype is not a credible utility because the specification does not identify any compounds that alter a phenotype of the mice.

Determining compounds that ameliorate a phenotype is not a specific or substantial utility because determining compounds that alter a phenotype may not reveal the function of the protein. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-13).

Thus, knockout mice may be used to identify compounds that bind to the knocked out gene ($GABA_B$ in the case of Bowery), but the identification of such compounds may not reveal the function of the protein (because Bowery identified agents that altered phenotypes but the functional properties of GABA subunits remained unknown). Determining compounds that ameliorate a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not mCAR2 itself. Determining compounds that ameliorate a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. As such, determining compounds that ameliorate a phenotype is not a specific or substantial utility.

Determining compounds that ameliorate a phenotype is not a substantial utility because compounds that alter a phenotype may not be therapeutic in humans. MacDonald (J. Biol. Chem., Nov. 22, 2002, Vol. 277, pg 44938-44945) identified a bispidine derivative (C-1) that antagonized Kv2.1 using different mouse cells, but taught that further experimentation was required to determine how to use bispidine derivatives to treat diabetes (see last ¶). Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) administered antagonists of $GABA_B$ receptor to $GABA_B$ -/- knockout mice, which caused decreased anxiety in various tests. While the antagonists were not found using the mice, they were found using *in vitro* assays (see pg 1058, col. 2, 1st full ¶, lines 4-8, and Urwyler *et al,* 2003, referred to therein). Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology.

Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). However, the art did not and does not teach using the antagonist to treat any disease. Thus, compounds that alter a phenotype in knockout mice may not be used for therapy in humans. Using the mouse to obtain clues of the role of the $GABA_B$ receptor in a molecular pathway of anxiety as taught by Mombereau or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of $GABA_B$ in the pathway. Too much further research would be required to determine whether "positive modulators" or "antagonists" that bind $GABA_B$ will treat anxiety or how to modify the compounds so that they can treat anxiety. Further research would be required to determine how to use agents identified using the mouse to treat disease, which is not a "substantial utility" (see Utility Guidelines under "substantial utility" - methods of determining a compound that itself has no "specific and/or substantial utility"). Therefore, determining agents that modulate the phenotype of a knockout mouse is not a substantial utility because the agent may only provide clues to the

function of the knocked out gene and may not be capable of treating disease in humans.

Knockout -/- or -/+ mCAR2 mice did not have a "well-known utility" to study the function of mCAR2. MPEP 2701 II(A)(3) requires a "well-established utility" must be a utility that is specific, substantial and credible. It was well known that knockout mice could be used for scientific research to study the function of a gene. However, scientific research is not the same as "patentable utility" or a "well-established" utility.

Olsen (GABA in the Nervous System, 2000, pg 81-95, also cited above) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to

determine the function of the gene. In fact, the function of the gene may never be determined from the knockout mouse. A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility." Using the mouse for further research is not a substantial utility, which is specifically described in the utility guidelines:

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study would have been required to determine how to use the -/- or -/+ mCAR2 mouse known in the art or of applicants' invention to determine the function of the gene. The overall phenotype of the applicants' mice does not correlate to Dent Disease or any other disorder. Therefore, further study would be required to determine the function of the mCAR2 gene or how to use the mice as a model for any disease. As such, using the mice claimed to determine the function of the mCAR2 is not a "substantial utility."

Applicant argues the mice have a well-established utility because a person of ordinary skill would immediately appreciate why the knockout mice were useful to define the function and role of the disrupted gene. Applicant points to an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-924), The Molecular

Biology of the Cell (Albert, 4th ed., Garland Science (2002)), Gene VII (Lewin, Oxford University Press (2000)), Joyner (Gene Targeting: A Practical Approach, Oxford University Press, 2000), Matise (Production of targeted embryonic stem cell clones in Joyner) and Crawley (What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss, 2000) to establish the mice had "well-established" utility. Applicants conclude the mice are useful for determining gene function (pg 10). Applicant's arguments are not persuasive.

First, the NIH report and Austin were not available until 2004 and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, a mouse with decreased performance on a rotarod, reduced spleen weight, lymphoid depletion in the spleen and thymus, and reduced thymus size and weight is not a model of any disease.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. Joyner states gene targeting in ES is used to study gene function in a mammalian organism. Matise states knockout ES cells can be used to study gene function in cell

culture and in vivo. Crawley states knockout mutations provide a means for understanding gene function. None of references teach the mice will determine the function of the gene. Applicants have used the mice in expression analysis and phenotype analysis tests, but the mice did not have any altered phenotype. Therefore, the mice do not even provide a clue as to the function of the mCAR2 gene. Applicants' research did not determine the function of the gene. As such, the mice claimed cannot be used to determine gene function because they do not even provide a clue as to the gene function.

The function of the mCAR2 gene may never be determined from the knockout mouse described by applicants that have numerous abnormalities that do not correlate to one gene function or one metabolic, immunologic or neurologic pathway. Knockout mice may never reveal the function of the mCAR2 gene (Olsen of record cited above). A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility" (see utility guidelines). A mouse requiring significant further research to determine the function of the gene that does not even provide a phenotypic clue to the specific pathway to which the gene may be involved does not rise to the level of a specific and substantial "well-established utility" as set forth by the utility guidelines.

Applicants compare the mice claimed to gas chromatographs, screening assays and nucleotide sequencing methods. Applicant's arguments are not persuasive. Gas chromatographs, screening assays and sequencing have specific, credible and substantial utilities. Gas chromatographs separate the chemical components of a

compound and identify them. Screening assays have various functions, but may be used, for example, to determine the amount of protein expression in a population of cells. Sequencing methods provide the nucleotide sequence of a nucleic acid molecule. Unlike gas chromatographs, screening assays or sequencing methods, the mice claimed may be used to generate data, but the data may not reveal the function of the gene or provide any substantially useful information. Evidence is provided by applicant's own data in which expression analysis and behavioral analysis generated data indicating the mice had decreased performance on a rotarod, reduced spleen weight, lymphoid depletion in the spleen and thymus, and reduced thymus size and weight, but the data does not reveal the function of SEQ ID NO: 1. Further research would be required to determine the function of SEQ ID NO: 1 using the phenotypic data provided by applicants. The utility guidelines state using a product for further research is not a "substantial" utility. In this case, the expression and phenotypic analysis provide clues that are so generic as to be meaningless. The function of a gene that causes decreased performance on a rotarod, reduced spleen weight, lymphoid depletion in the spleen and thymus, and reduced thymus size and weight cannot be guessed. Therefore, using the mouse claimed as a research tool, specifically for expression and phenotypic analyses, does not provide any substantial utility.

Applicants argue mice actually being used must have a real world use. Applicant's argument is not persuasive. Just because the mice are in use in the industry in 2005 does not mean the specification as originally filed disclosed a "real world use." The industry may have determined how to use the mice since the time of

filing. Furthermore, just because the mice were used in expression and phenotyping analyses does not indicate that using the mice in such analyses had substantial, specific and credible utility. That is because the data in this case did not reveal the function of the mCAR2 gene or that the mouse was a model of any disease. The utility guidelines indicate a "real world use" must be substantial, specific and credible. In this case, merely studying a gene using a knockout mouse is not a substantial "real world use" because the gene does not have a patentable utility, because further research does not constitute a patentable utility and because the mouse may never reveal the function of the gene. Nowhere has applicants pointed to one specific assay that has a substantial use in which the mice claimed are used by the industry or that correlates the data to a specific disease condition or gene function. Nowhere has the applicant pointed to one piece of data that can be correlated to a disease state or that is capable of revealing the specific function of the mCAR2 gene. Therefore, it is not readily apparent that the mice claimed have a "real world use" that is substantial, specific and credible.

Applicants arguments regarding "specific utility" are noted but do not address the specific role of mCAR2 in a generic pathway or how agents identified using the mouse by determining changes in phenotype may actually be modulating other proteins in a generic pathway in which mCAR2 is involved. Applicants discussion of using the mice to study gene expression under the heading of "specific utility" is noted (pg 13) but does not appear to correlate to any "specific utility" rejections (using mice merely for gene expression analysis does not have substantial utility).

Using the mice "to study gene function" is so general as to be meaningless because the function may never be revealed. Applicants used the mice in various assays but did not determine the function of the mCAR2 gene. Merely suggesting the mice should be used as a starting point for further research without providing the end point of any research effort does not rise to the level of a substantial utility. Applicants have at best i) provided a "laundry list" of assays the mice can be used in, each general and speculative, ii) used the mice in phenotyping assays without revealing the function of the mCAR2 gene, and iii) used the mice in expression analysis assays without revealing the function of the mCAR2 gene.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure for the mice claimed. Applicants' arguments are not persuasive. Mice without a phenotype as encompassed by claims 53-57 do not provide any clues as to the function of the mCAR2 gene. The mice with abnormal phenotypes in claims 40-50 do not even provide a clue as to a pathway in which the gene is related because they are generic to performance in a rotarod test, spleen weight, lymphoid numbers in the spleen and thymus, and thymus size and weight. Significant further research in this case is required to use the mice claimed to determine the function of the mCAR2 gene. In *En re Brana*, the applicants disclosed compounds that were effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The mice claimed in the instant application do not correlate to the compounds described by Brana because i) the mice are not used for treating disease, ii) the mice merely provide a clue that the

mCAR2 relates to performance on a rotarod, spleen weight, lymphoid amounts in the spleen and thymus, and thymus size and weight without revealing the function of mCAR2 or the role of mCAR2 in those areas, iii) the mice provide a clue that the mCAR2 is generic to performance on a rotarod, spleen weight, lymphoid amounts in the spleen and thymus, and thymus size and weight without correlating the role of mCAR2 in each pathway, and iv) mice with decreased performance on a rotarod, reduced spleen weight, lymphoid depletion in the spleen and thymus, and reduced thymus size and weight are not a model of disease in humans. Therefore, comparing the mice to the anti-tumor compounds in *En re Brana* is improper.

Applicants are reminded that In re Schoenwald, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. In this case, the mouse claimed might only provide a clue to a developmental process or signal transduction pathway in which SEQ ID NO: 1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO: 1 is involved in development or signal transduction pathway. The phenotype provides only a clue that SEQ ID NO: 1 is generically involved in development or a signal transduction pathway influenced by numerous proteins.

Claim Rejections - 35 USC § 112

Enablement

Claims 40-50 and 53-57 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having abnormal pain threshold for reasons of record.

Applicants refer to the arguments provided under the utility rejection. Applicants' arguments are not persuasive for reasons cited above.

New Matter

Claims 40-50 and 53-57 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "mCAR2 gene" in claim 53 is new matter. Pg 6, lines 24-29, describes a "nuclear hormone receptor gene" as being "a sequence comprising SEQ ID NO: 1 or... ... isoform mCAR2 identified in Genebank as Accession No.: AF009328; GI NO: 2267577." Nowhere does the specification refer to the genus mCAR genes. The specification only contemplates the species of SEQ ID NO: 1 within the genus "mCAR2 gene." The specification does not contemplate the broad genus of any mCAR2 gene, any "endogenous" mCAR2 gene or teach any other mCAR2 sequences other than SEQ ID NO: 1. Applicants have not addressed this rejection.

The phrase "null allele" in claim 53 is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed.

A "null allele of the endogenous mCAR2 gene" in claim 53 as amended is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The specification does not distinguish the genus of "endogenous" mCAR2 genes.

The phrase "selectable marker" in claim 56 is found on pg 7, line 15.

Indefiniteness

Claims 40-50 and 53-57 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection regarding "a gene encoding mCAR2" in claim 39 has been withdrawn because the claim has been canceled.

The metes and bounds of a "mCAR2 gene" in claim 53 as newly amended remain indefinite for reasons of record. The specification defines a nuclear hormone receptor gene as "a sequence comprising SEQ ID NO: 1 or comprising the sequence encoding the orphan nuclear hormone receptor isoform mCAR2 identified in Genebank as Accession No.: AF009328, GI: NO: 2267577. In one aspect, the coding sequence of the nuclear hormone receptor gene comprises SEQ ID NO:1 or comprises the nuclear hormone receptor gene identified in Genebank as Accession No.: A17009328; GI: NO:

2267577" (pg 6, lines 24-29). The paragraph bridging pg 4-5 states a gene is any DNA that shares homology with the complement of any sequences disclosed in the specification. However, it cannot be determined how much homology is required for a sequence to still be considered a mCAR2 gene. As such, the metes and bounds of genes that are mCAR2 genes cannot be determined.

The rejection regarding the metes and bounds of a "null allele" in claim 53 has been withdrawn. Genes VII (2000) taught that additional DNA could be introduced into a gene to prevent its expression and to generate a null allele. Breeding of animals with a null allele can generate a knockout having no active copy of the gene. Hasty (2000) taught the strategy of ablating the function of a target gene was a null allele.

Claims 41-50 remain indefinite because the metes and bounds of what applicants consider an "abnormality" cannot be determined. The term "abnormal" is subjective and is not defined in the specification and is a subjective term in the art. Applicants have not addressed this rejection.

Claim Rejections - 35 USC § 102

Claims 53-57 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kato (J. Biochem., May 2000, Vol. 127, pg 717-722) supported by Li (PNAS, Sept. 1997, Vol. 94, pg 9831-9835) for reasons of record.

Kato taught heterozygous and homozygous mice having a disruption in the nuclear hormone receptor gene VDR. The VDR gene is an mCAR2 gene because i) the definition of "nuclear hormone receptor" on pg 6 does not define "mCAR2 genes" or

limit the mCAR2 gene to SEQ ID NO: 1 and ii) the definition of "gene" on pg 4, line 29, through pg 5, line 2, encompasses any DNA sequence that hybridizes to complement of SEQ ID NO: 1. Li was cited by Kato in the first sentence of the paragraph bridging pg 718-719 (26) and supports the fact that the disruption was inherently made using the neomycin resistant gene (pg 9831, col. 2, "Generation of VDR Null Mice"; "...16 of which had a single copy of the neomycin resistance gene").

Claims 40-50 have been withdrawn because one of skill would not reasonably conclude that mice with bone and parathyroid abnormalities, hair loss and increased immunoreactive PTH levels as taught by Kato would have decreased performance on a rotarod test, decreased spleen size or weight, spleen to body weight ratio, lymphoid depletion of the spleen or thymus, reduce thymus size or weight or reduced thymus to body weight ratio as claimed.

Applicants argue the VDR gene is not an endogenous mCAR2 gene as claimed. Applicants' argument is not persuasive. The VDR gene is "endogenous" because it is found in the mouse. The VDR gene is an mCAR2 gene because i) the definition of "nuclear hormone receptor" on pg 6 does not define the term "mCAR2 gene" or limit the mCAR2 gene to SEQ ID NO:1 and ii) the VDR gene hybridizes to the complement of SEQ ID NO: 1 and meets applicants definition of "gene" definition of "gene" (pg 4, line 29, through pg 5, line 2).

Claim Rejections - 35 USC § 103

Claims 53-57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kato (J. Biochem., May 2000, Vol. 127, pg 717-722) supported by Li (PNAS, Sept. 1997, Vol. 94, pg 9831-9835) in view of Choi (J. Biol. Chem., 1997, Vol. 272, pg 23565-23571) for reasons of record.

Kato taught heterozygous and homozygous mice having a disruption in the nuclear hormone receptor gene VDR. Li was cited by Kato in the first sentence of the paragraph bridging pg 718-719 (26) and supports the fact that the disruption was inherently made using the neomycin resistant gene (pg 9831, col. 2, "Generation of VDR Null Mice"; "...16 of which had a single copy of the neomycin resistance gene." Kato did not teach disrupting SEQ ID NO: 1.

However, Choi taught the nucleic acid sequence of the mouse nuclear hormone receptor gene of SEQ ID NO: 1.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in a nuclear hormone receptor gene as taught by Kato wherein the gene was the nuclear hormone receptor of SEQ ID NO: 1 taught by Choi. One of ordinary skill in the ad at the time the invention was made would have been motivated to disrupt SEQ ID NO: 1 instead of the VDR nuclear hormone receptor gene taught by Kato to gain clues to the function of SEQ ID NO: 1 in vivo.

Claims 40-50 have been withdrawn because one of skill would not reasonably conclude that mice with bone and parathyroid abnormalities, hair loss and increased immunoreactive PTH levels as taught by Kato would have decreased performance on a

rotarod test, decreased spleen size or weight, spleen to body weight ratio, lymphoid depletion of the spleen or thymus, reduce thymus size or weight or reduced thymus to body weight ratio as claimed.

Applicants argue the references combined are not enabling to produce the claimed mouse because the references do not teach the genomic sequence of the mCAR2 gene. Applicants' argument is not persuasive. One of ordinary skill in the art would have had a reasonable expectation of successfully making an ES cell with a disruption of a mCAR2 gene using the cDNA of Choi because methods of making knockout mice using the cDNA were known in the art. Smart (Neuron, April 1998, Vol. 20, pg 809-819), Scrocchi (Nature Med., Nov. 1996, Vol. 2, No. 11, pg 1254-1258) and Varfolomeev (Immunity, Aug. 1998, Vol. 9, pg 267-286) used cDNA to isolate genomic sequence of a gene and how to make a targeting construct using the genomic sequence, map the gene and construct a targeting vector using that information (Scrocchi, pg 1257, col. 2, "Targeting vector;" Varfolomeev, pg 273, last 4 lines, through pg 274, col. 2, line 7). Thus, Smart, Scrocchi and Varfolomeev support the fact that it was well within the knowledge of those of ordinary skill in the art at the time of filing to use the cDNA of Choi to isolate genomic sequence of the mCAR2 gene and make the mouse claimed. Applicants have not provided any reason why the cDNA of Choi could not be used to isolate the genomic sequence of the mCAR2 gene using the methods known in the art described for example by Smart, Scrocchi and Varfolomeev.

Applicants argue the 103 contradicts the utility rejection (pg 22 of response). Applicants' argument is not persuasive. The examiner has provided adequate

reasoning to support both the 101 and 103 rejections. The desire of those of ordinary skill to gain clues as to the function of genes was well established at the time of filing. The fact that those of ordinary skill in the art desired to make knockout mice to gain clues as to the function of genes does not necessarily mean the mice would have a specific and substantial utility, i.e. that those of ordinary skill would determine the function of the gene from the clues provided by the mice. Evidence is provided by applicants who used the mice in various tests and gained clues regarding the gene but did not teach the function of the gene.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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